

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 3

Limpet Hemocyanin or a derivative thereof.

F3  
cont

76. (New) The composition of claim 53 wherein the conjugation of the ganglioside involves a ceramide double bond of the ganglioside and an aminolysl group of Keyhole Limpet Hemocyanin or a derivative thereof.

#### REMARKS

Claims 53-71 were pending in the subject application. Applicants have hereinabove amended claims 53 and 65 and added new claims 72-76. Applicants contend that this does not raise any issue of new matter. Support for these claims may be found inter alia in the specification on page 32, line 1 to page 33, line 10. Accordingly, claims 53-76 will be pending upon entry of this amendment.

#### Objection to the Disclosure

The Examiner stated that the prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No. 9). The Examiner stated that applicants submit they will submit a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner stated that until applicants submit a proper Figure said objection is maintained.

In response, applicants will provide a new figure 6B upon the indication of allowable subject matter.

#### Double patenting

The Examiner stated that claims 53-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims 1-4, 6-20 and 44-52 of copending Application No. 08/475,784 for the reason set forth in the last Office Action.

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 4

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The Examiner stated that claims 53-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44 and 46-56 of copending Application Nos. 08/477,147 and 08/482,809.

The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Actions.

The Examiner stated that applicants argue that they will add new claims in US 08/475,784; 08/477,147 and 08/481,089 and that they believe the added new claims in the applications will obviate the obvious type double patenting. The Examiner stated that applicants arguments are noted. The Examiner stated that however, until said claims are added said rejection is maintained for the reasons of record. The Examiner stated that furthermore, the Examiner suggests that applicants provide a copy of the claims in the copending applications in the next Office Action.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, without conceding the correctness of the Examiner's position but to expedite the prosecution of the subject application, applicants added new claims in the subject application and in U.S. Serial Nos. 08/475,785, 08/477,147 and 08,481,089. Applicants contend that the addition of these new claims obviates the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

**Rejection Under 35 U.S.C. §112, First Paragraph**

The Examiner stated that claims 53-56 and 58-71 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 5

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6/10/96 (see Paper No. 9).

The Examiner stated that applicants' amendment is sufficient to obviate the objection to the specification for: 1) the use of other ganglioside or chemically modified ganglioside; and 2) use of the claimed product as a vaccine. The Examiner stated that however, the specification provides insufficient guidance of how to use derivatives of KLH as recited. The Examiner stated that applicants assert that by routine experimentation one skilled in the art is enabled to make derivatives of KLH (see applicants arguments on Paper No. 12; page 4). The Examiner stated that applicants assert that the derivatives of KLH can be tested using the KLH disclosed in the specification. The Examiner stated that applicants arguments are not persuasive.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. The Examiner stated that for example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not effect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). The Examiner stated that Rudinger et al. Teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstakingly experimental study" (see page 6). The Examiner stated that Salgaller et al teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. The Examiner stated that Fox et al. Teach methods for determining fragments which have antigenic activity is unpredictable. The Examiner stated that these

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 6

references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The Examiner stated that contrary to applicants arguments it is reasonable to conclude an undue burden is required to screen for positions within the sequence where amino acid modifications (i.e. additions, deletions or modifications) can be made with a reasonable expectation of success of obtaining similar activity/utility are limited and the result of such modifications is unpredictable as exemplified by the teachings of Lazar et al., Burgess et al., Rudinger et al., and Salgaller et al. The Examiner stated that these references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

The Examiner stated that the specification does not support the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions which can be predictably modified; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The Examiner stated that thus, applicants have not provided

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 7

sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions, and/or substitutions of any size. The Examiner stated that the scope of the claims must bear a reasonable correlation with the scope of enablement (in re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The Examiner stated that see ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

The Examiner stated that applicants cite to page 12, lines 4-13 of the specification for support of using derivatives of KLH. The Examiner stated that said disclosure is not commensurate in scope with the claimed invention. The Examiner stated that said cite makes reference only to linking KLH to an "immunological adjuvant" **and not** amino acid modifications (i.e. deletions, substitutions) of KLH. The Examiner stated that as set forth above the scope of the claims must bear a reasonable correlation with the scope of enablement (in re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that for the reason set forth above and in the last Office Action said rejection is maintained.

In response, applicants respectfully traverse the above rejections. Applicants point out that the claims do not contain the language "KLH derivatives." Applicants point out that claim 53 is directed to the following:

A composition comprising a GM2 or GD2 ganglioside conjugated through the ceramide portion of the ganglioside to an immunogenic protein and a carbohydrate derivable from the bark of a Collage saponaria Molina tree, the amounts of such conjugated ganglioside and such carbohydrate being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier.

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 8

Accordingly, there is no issue of KLH derivatives in these claims. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

**Rejection Under 35 U.S.C. §112, First Paragraph**

The Examiner stated that claims 53-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the original specification does not provide an adequate written description of conjugation a ceramide portion of the GM2 or GD2. The Examiner stated that the specification as originally filed only provides support of conjugating GD3 by the ceramid portion (see page 32). The Examiner stated that the Examiner acknowledges applicants remarks for support of claimed subject matter. The Examiner stated that however, applicants remarks are directed to claims canceled. The Examiner stated that the Examiner invites applicants to point by page and line number for conjugating GM2 or GD3 by the ceramide portion as newly submitted.

In response, applicants respectfully traverse the above rejection. Applicants contend that the specification conveys to one skilled in the art that applicants had possession of the claimed subject matter at the time of filing. Applicants respectfully direct the Examiner's attention to page 32, lines 13-18 of the specification. Applicants maintain that this teaches a general method for the conjugation of gangliosides through the ceramide portion. Applicants contend that one skilled in the art would understand that this approach would be applicable to other

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 9

gangliosides, not just GD3. Applicants contend that conjugations of other gangliosides were envisioned at the time of filing, as evidenced by the disclosure on page 12, lines 22-26. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw the rejection.

Ritter et al

Applicants acknowledge the Examiner's statements that the prior art made of record and not relied upon is considered pertinent to applicant's disclosure and Ritter et al (Exhibit 13) discloses of a GD3 amide derivative and that said derivatives had the highest antibody response.

Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of objection and rejection be reconsidered and withdrawn and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Applicants : Philip Livingston and Friedhelm Helling  
U.S. Serial No.: 08/477,097  
Filed : June 7, 1995  
Page 9

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.



Respectfully submitted,

*Albert Wai-Kit Chan*

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

*Albert Wai-Kit Chan* 5/17/99  
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